

Claims

1. A process for the preparation of multiple cross-linked derivatives of hyaluronic acid, which process comprises covalently cross-linking HA via two or more different functional groups, wherein said cross-linking is effected by contacting HA with one or more chemical cross-linking agents so as to form two or more chemically distinct cross-links, between said HA molecules
2. A process according to claim 1 wherein the functional groups are selected from hydroxyl, carboxyl and amino.
3. A process according to claim 1 or claim 2 wherein the crosslinking is effected by means of two or more different bonds selected from ether, ester, sulfone, amine, imino and amide bonds.
4. A process according to any of claims 1 to 3 wherein the cross-linking agent is selected from formaldehyde, glutaraldehyde, divinyl sulfone, a polyanhydride, a polyaldehyde, a polyhydric alcohol, carbodiimide, epichlorohydrin, ethylene glycol diglycidylether, butanediol diglycidylether, polyglycerol polyglycidylether, polyethylene glycol diglycidylether, polypropylene glycol diglycidylether, or a bis-or poly-epoxy cross-linker.
5. A process according to any of claims 1 to 4 wherein an ether bond is formed using a crosslinking agent selected from bis and poly epoxides under alkaline conditions.
6. A process according to any of claims 1 to 4 wherein an ester bond is formed using a crosslinking agent selected from bis and poly epoxides under acidic conditions.
7. A process according to claim 5 or claim 6 wherein the crosslinker is selected from 1,2,3,4-diepoxybutane and 1,2,7,8-diepoxyoctane.
8. A process according to any of claims 1 to 4 wherein an ether bond is formed using a glutaraldehyde cross-linking agent under acidic conditions.

*Sub
a²
cont*
9. A process according to any of claims 1 to 8 wherein the crosslinking of each type of functional group is effected sequentially.

10. A process according to claim 9 which comprises cross-linking HA via a first functional group and subsequently further cross-linking the product via a second functional group, wherein said first and second functional groups represent different chemical entities.

*Sub
a³*
11. A process according to claim 9 or claim 10 wherein HA is first cross-linked via the hydroxyl groups by formation of ether bonds and subsequently cross-linked via the carboxyl groups by formation of ester bonds.

*Sub
a⁴*
12. A process according to any of claims 1 to 8 wherein the crosslinking of each type of functional group is effected simultaneously.

*Sub
a⁵*
13. A process according to any of claims 1 to 12 for preparing double crosslinked HA.

14. A process according to claim 13 which comprises:
(a) cross-linking HA via a first functional group and
(b) subsequently further cross-linking the product of (a) via a second functional group, wherein said first and second functional groups represent different chemical entities.

*Sub
a⁶*
15. Multiple cross-linked HA obtainable by a process according to any of claims 1 to 14.

16. HA cross-linked to a further molecule of HA wherein the HA is crosslinked by at least two different types of bond.

*Sub
a⁷*
17. Cross-linked HA according to claim 15 or claim 16 wherein the crosslinking bonds are selected from two or more of ether, ester, sulfone, amine, imino and amide bonds.

*Sub
a⁸*
18. Multiple cross-linked HA according to any of claims 15 to 17 in the form of a film.

*Sub
a⁹*
19. Multiple cross-linked HA according to any of claims 15 to 17 in the form of a gel.

Sub
a/b

20. HA according to any of claims 15 to 19 which is double cross linked HA.

Sub
all

21. A product comprising multiple cross-linked HA according to any of claims 15 to 20.

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22. The use of HA according to any of claims 15 to 20 in the preparation of a product for pharmaceutical, cosmetic or medical use.

23. The use of HA according to any of claims 15 to 20 or a product according to claim 21 in medicine or surgery.